Glucagon as a therapeutic agent in the treatment of asthma.

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Glucagon, an activator of cyclic AMP that produces smooth muscle relaxation, was studied to determine if it had the ability to reverse or modify the degree of bronchospasm in asthmatic patients. Fourteen patients with mil to moderately severe bronchospastic exacerbation of asthma were studied using peak expiratory flow rates (PEFR) before and after receiving one milligram of glucagon intravenously. Eight (57%) of the 14 patients demonstrated a mean PEFR increase of 113 L/min ten minutes following glucagon administration and were termed responders. This study suggests that further investigation of the role of glucagon in asthmatic patients is warranted.

PMID: 2362112 [PubMed - indexed for MEDLINE]

1: Am J Emerg Med. 1998 May;16(3):272-5.

Nebulized glucagon in the treatment of bronchospasm in asthmatic patients.

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This study sought to determine if nebulized glucagon, a well-known smooth muscle relaxant, is effective in relieving asthmatic bronchospasm. Ten subjects, aged 12 to 26 years, with chronic stable asthma were studied in a pulmonary function laboratory under a randomized double-blind, placebo-controlled, crossover design. Bronchospasm was induced in each subject with progressive doses of nebulized methacholine until forced expiratory volume in 1 second (FEV1) had decreased at least 20% from baseline. Subjects then received either nebulized saline or 2 mg of nebulized glucagon. Spirometry was performed at 5, 15, and 30 minutes after treatment. Subjects then received 2.5 mg of nebulized albuterol and had spirometry 15 and 30 minutes thereafter. Each subject returned for testing with the alternative solution at least 1 week later. Treatment with nebulized glucagon resulted in a 58% +/- 15% improvement in FEV1 15 minutes after treatment compared with 36% +/- 7% after nebulized saline ($P < .05$). No adverse effects of glucagon treatment occurred. This study suggests that nebulized glucagon reduces methacholine-induced bronchospasm in asthmatic patients.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 9596431 [PubMed - indexed for MEDLINE]

1: Eur J Respir Dis Suppl. 1983;128 (Pt 2):427-9. Related Articles, Link

Pretreatment of exercise-induced asthma with inhaled vasoactive intestinal peptide (VIP).

Bundgaard A, Enehjelm SD, Aggestrup S.

PMID: 6578098 [PubMed - indexed for MEDLINE]

1: Ann Neurol. 1988;23 Suppl:S71-3.

AIDS and its dementia as a neuropeptide disorder: role of VIP receptor blockade by human immunodeficiency virus envelope.

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The CD4 molecule was originally described as a marker for a subset of lymphocytes; however, recent work has shown that a similar, if not identical, molecule is present on human brain. We have realized that this cell-surface recognition molecule is normally modulated by vasoactive intestinal peptide (VIP), one of the 50 or more neuropeptides that compose a shared intercellular network joining the brain, glands, and immune system. Human immunodeficiency virus (HIV), the etiological agent of acquired immunodeficiency syndrome (AIDS), has been found to mimic VIP binding via peptide T (4-8), a pentapeptide sequence present in approximately the same region of all 20 HIV isolates whose sequences are currently known. AIDS dementia results from interference of gp120, present on the HIV envelope protein, with normal VIP-ergic neurotrophic effects, and effects on cerebral blood flow.

PMID: 2831805 [PubMed - indexed for MEDLINE]

1: Endocrinology. 1994 May;134(5):2121-5.

Stearyl-norleucine-vasoactive intestinal peptide (VIP): a novel VIP analog for noninvasive impotence treatment.

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The present report relates to pharmaceutical composition for the treatment of male impotence. The transdermal application of a potent derivative of vasoactive intestinal peptide (VIP) coupled to a suitable hydrophobic moiety (e.g. stearyl-VIP) in a suitable ointment composition (e.g. Sefsol) enhances sexual activity and erection formation in a variety of impotence models in rats (sterile rats, diabetic rats, and animals with high blood pressure). Furthermore, exchange of the methionine in position 17 with norleucine enhances biological activity. Thus, stearyl-Nle17-VIP may be considered useful for the treatment of impotence.

PMID: 8156912 [PubMed - indexed for MEDLINE]

1: AJR Am J Roentgenol. 1994 Feb;162(2):325-8. Related Articles, Link

Treatment of acute esophageal food impaction with glucagon, ar effervescent agent, and water.

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OBJECTIVE. In 1990, we described a combination therapy that uses glucagon, an effervescent agent, and water to relieve acute esophageal food impaction. The initial trial showed relief of the obstruction in 12 of 16 cases without complication, so we continued the series to determine the safety and effectiveness of this technique. SUBJECTS AND METHODS. Between July 1987 and August 1993, a prospective trial consisting of 43 patients with 48 episodes of acute (less than 24-hr duration) food impaction in the distal two thirds of the esophagus were identified with either a barium or water-soluble contrast agent swallow. Subsequently, we attempted to relieve the obstructio by using 1 mg of IV glucagon, an effervescent agent, and water. A water-soluble esophagogram was obtained immediately in all cases to determine th response to the therapeutic intervention and to look for any complication suc as perforation. RESULTS. The combination therapy resulted in the clearance of food obstruction in 33 (69%) of 48 attempts. One complication, a minor mucosal laceration, occurred after two unsuccessful treatments. A lower esophageal ring was the single most common abnormality identified (n = 24) The average width of rings in the successful cases was 15.4 mm and the average in the unsuccessful cases was 13 mm. Other underlying causes of obstruction were esophagitis and stricture. CONCLUSION. Our experience with the use of glucagon, an effervescent agent, and water to relieve acute esophageal food impaction indicates that the technique is highly successful and that serious complications are rare.

PMID: 8310919 [PubMed - indexed for MEDLINE]

1: Acta Paediatr. 2002;91(5):540-5.

Multiple doses of secretin in the treatment of autism: a controlled study.

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Dramatic effects on autistic behaviour after repeated injections of the gastrointestinal hormone secretin have been referred in a number of case reports. In the absence of curative and effective treatments for this disabling condition, this information has created new hope among parents. Although controlled studies on the effect of mainly one single dose have not documented any effect, many children still continue to receive secretin. Six children enrolled in a double-blind, placebo-controlled crossover study in which each child was its own control. Human synthetic secretin, mean dose 3.4 clinical units, and placebo were administered intravenously in randomize order every 4th wk, on three occasions each. The measurement instruments were the visual analogue scale (VAS) and the aberrant behaviour checklist (ABC). Statistically significant differences were found for placebo in 3 out o 6 children and for secretin in one child, using parental ratings only (VAS scores). Differences were small and lacked clinical significance, which was i accordance with the overall impression of the parents and teachers and visual inspection of graphs. Conclusion: In this placebo-controlled study, multiple doses of secretin did not produce any symptomatic improvement.

Publication Types:
- Clinical Trial
- Randomized Controlled Trial

PMID: 12113323 [PubMed - indexed for MEDLINE]

Press Release for *Nature Medicine*: May 2001

PLEASE QUOTE *Nature Medicine* AS THE SOURCE OF THESE ITEMS

Peptide cures arthritic mice

Rheumatoid arthritis (RA) is an inflammatory joint disease characterized by pain, swelling, stiffness, and loss of function of joints, typically those in the wrist and hand. The inflammatory process eventually destroys cartilage and bone in the joints. The disease often affects the wrist joints and the finger joints closest to the hand. Around 40 million Americans suffer from RA.

The cause of RA is unknown, and treatment is aimed at pain control since no cure is available. However, based on experiments to be reported in the May issue of Nature Medicine, a team of scientists at Complutense University in Spain believe that a neuropeptide could be used to treat the disease effectively.

Using a mouse model of RA, Mario Delgado and colleagues discovered that injections of vasointestinal peptide (VIP) delayed onset of the disease by reducing the severity of arthritis, and preventing joint swelling and destruction of cartilage and bone. VIP-treated mice suffered no remission two weeks after stopping injections and VIP improved disease that was already established.

The scientists believe that VIP works by decreasing the production of inflammatory cytokines and by modulating the action of inflammatory lymphocytes known as Th1.

Gary Firestein from University of California, San Diego, discusses the findings in a *News & Views* article. He points to potential pitfalls of using the peptide for therapy, such as gastrointestinal side effects, but ultimately concludes that the risk:benefit ratio is a favorable one since the condition affects so many people.

Protein responsible for failing heart

Heart failure-when the heart can not supply sufficient blood to organs of the body-affects around 4.5 million patients in the US. One of the ways in which it occurs is through inappropriate dilation of heart chambers such as the atria and the ventricles. This enlargement (dilated cardiomyopathy) is due to growth of individual heart cells and can be caused by genetic mutation or by disease.

Scientists at the University of California, San Diego School of Medicine have investigated mutations of the cytoskeleton (the internal system of protein fibres and tubules within the cell) that lead to dilated cardiomyopathy.

Using a mouse model, they discovered that a protein called alpha-actinin-associated LIM protein (ALP) is vital to the development of the right ventricle. Disruption of the ALP gene causes dilation and dysfunction of the right ventricle indicating that that ALP might be involved in some cases of cardiomyopathy. They report that ALP enables alpha-actinin to cross-link actin filaments within the heart that provide structural support to cells and together, allowing the heart to contract and relax.

Yeast: the basis for powerful new vaccines

Vaccines that cause the production of antibodies alone to menacing antigens are not powerful enough to combat diseases such as HIV and cancer. Thus, scientists are currently trying to develop vaccines that stimulate the second half of the immune response called the cell-mediated response. The latter involves the stimulation of cells called cytotoxic T lymphocytes that produce chemicals that kill the offending pathogen. Richard Duke and colleagues at Ceres Pharmaceuticals have developed the prototype for such a vaccine using the simple yeast.

The scientists engineered yeast cells to express an HIV antigen. They vaccinated mice with the yeast vaccine and discovered that the cytotoxic T lymphocytes that the mice produced were powerful and specific enough to destroy only those cells containing a fraction of the HIV virus.

The novel yeast vaccine works by activating a group of immune cells called dendritic cells (DC). These cells absorb the yeast and any antigens it is carrying, process the antigens and then present them on the cell surface. This triggers a strong immune reaction which also includes the release of a potent chemical called interleukin-12.

The authors propose that such a yeast vaccine could be used

to immunize against several different types of cancers and infectious diseases.

Carbon monoxide can be good for you.

Although it has long been thought of as poisonous, deadly gas, scientists are now discovering that carbon monoxide (CO) could actually be therapeutic to the body at the right concentrations under conditions.

CO is synthesized by an enzyme called heme oxygenase type 1 (Ho-1) in response to conditions of low oxygen. David Pinsky and colleagues at Columbia University, New York discovered that mice lacking the gene for this enzyme whose lungs have been starved of blood and oxygen were able to recover by inhaling the gas. They further discovered that CO activates a system involving soluble guanylate cyclase which in turn supresses plasminogen activator inhibitor-1 (PAI-1). This allows the fibrinolytic cascade of enzmes which break down blood clots to become activated. Thus at sublethal doses, CO can save tissue that would otherwise die.

Christoph Thiemermann from the William Harvey Research Institute in London, adds balance to the research in an accompanying *News & Views* article, where he advises that the dangers of CO inhalation outweigh the benefits and we should not rush to treat patients with the deadly gas. He also compares the biological function of CO with that of another colorless water-soluble gas that has recently been found to have a major role in cardiovascular physiology-nitric oxide.